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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,953	04/08/2004	Jordan J. N. Tang	2932.1008-009	9733

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EXAMINER	
MOHAMED. ABDEL A	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 06/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/820,953	TANG ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT OF PRELIMINARY AMENDMENT, SEQUENCE LISTING, IDS, STATUS OF THE APPLICATION AND CLAIMS

1. The preliminary amendment, the Sequence Listing, the Information Disclosure Statements (IDS) and Form PTO-1449 filed 04/08/04 and 07/27/04, respectively are acknowledged, entered and considered. This is a Continuation of parent application Serial No. 09/603,713, filed 6/27/00, which claims the benefit of U.S. provisional applications Serial Nos. 60/141,363, 60/168,060, 60/177,836, 60/178,368, and 60/210,292, filed 16/28/99, 11/30/99, 1/25/00, 1/27/00, and 6/8/00, respectively. In view of Applicant's request, the computer-readable form of the sequence listing of the parent application Serial No. 09/603,713, filed 6/27/00 has been transferred to the instant application Serial No. 10/820,953, filed 04/08/04 since the computer-readable form of the sequence listing of this application is identical to that in the parent application 09/603,713. Thus, in accordance with 37 C.F.R. 1.821(e), the computer-readable form of the sequence listing filed in the parent application has been entered and considered in the instant application.

In regard to IDS filed 07/27/04, in view of Applicant's request, the references cited therewith in Form PTO-1449 are not provided in the instant specification. However, as per Applicant's request, since the cited references were considered previously in the parent application Serial No. 09/603,713, pursuant to 37 CFR § 1.98(d), the references cited in Form PTO-1449 in this application have been considered and signed as requested by Applicant. In view of Applicant's request,

claims 1-23 have been canceled and claims 24-38 have been added. Thus, claims 24-38 are now pending in the application.

ELECTION/RESTRICTION

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 24-32, drawn to a compound comprising a formula of claim 24 and a method for treating a patient to decrease the likelihood of developing or the progression of Alzheimer's disease by administering the compound thereof, classified in class 514, subclass 12.

II. Claims 33-38, drawn to a method of preparing a Leu* Ala dipeptide isostere, classified in class 435, subclass 68.1.

3. The inventions are independent or distinct, each from the other because:

Inventions II and I are distinct one from the other; Inventions are distinct because they have different structure, mode of operation, different function and different effects. Further, preparing a Leu* Ala dipeptide isostere has different starting materials and protecting groups than the compound of Group I. Furthermore, the library and computer searches are not coextensive. A reference, which would make obvious claims drawn to one the inventions may not obviate claims drawn to the other invention, absent ancillary evidence.

4. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and because the search for individual subject groups are not coextensive, restriction for examination purpose as indicated is proper.

5. During a telephone conversation with Karen Dow on 06/12/06 a provisional election was made with traverse to prosecute the invention of Group I, claim 24-32. Affirmation of this election must be made by Applicant in replying to this Office action. Claims 33-38 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Thus, the Office action is directed to the merits of claims 24-32 as *per* elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

OBJECTION TO THE SPECIFICATION AND DRAWING

7. The continuity data of the application should be updated in the specification (e.g., the status of the parent application Serial Number 09/603,713 should be identified). Further, Figure 8 is objected because Figure 8 needs SEQ ID NO: description. Appropriate correction is required.

OBJECTION TO TRADEMARKS AND THEIR USE

8. The use of the trademarks "FPLC RESOURCE-Q™", "SEPHACRYL™ S-300" and "Resource-Q®" have been noted in this application. The trademark "Resource-Q®" has not been capitalized, it should be capitalized whenever it appears and be accompanied by the generic terminology. Although, the use of trademarks are permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in a manner, which might adversely affect their validity as trademarks. Further, the specification, which specifies the generic terminology should include, published product information sufficient to show that the generic terminology or the generic description are inherent in the article referred by the trademarks. These description requirements are made because the nature and composition of article denoted by trademarks can change and affect the adequacy of the disclosure.

CLAIMS REJECTION-35 U.S.C. 112 1st PARAGRAPH.

9. Claims 24-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound having a structure of OM99-2 and a pharmaceutical acceptable salts thereof, does not reasonably provide enablement for a compound having a K_i of less than or equal to 1 nM for memapsin 2 as claimed in claim 27 because the specification on page 6, lines 17 to 18 discloses that the compound has 1.6×10^9 M, and a such, 1.6 nM is greater than 1 nM, and to a method for treating a patient to decrease the likelihood of developing or progressing of Alzheimer's disease

by administering to the individual an effective amount of compound of claim 24 in the manner claimed in claims 30-32. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not adequately teach an inhibitor of catalytically active memapsin 2 product defined by reference to a desirable characteristic or property by fitting into the catalytic cleft of memapsin 2 useful for treatment and/or prevention of Alzheimer's disease as presently claimed in claims 30-32; rather, the specification teaches the use of memapsin 2 in a method of cloning (Example 1), distribution (Example 2), expression, refolding and purification (Example 3), proteolytic activity (Example 4), activation (Example 5), Expression in mammalian cells (Example 6), design and synthesis (Example 7), and measurement of enzymatic activity *in vitro* (Example 8).

Therefore, the instant specification does not commensurate with the claimed subject matter in which the compound used as potent inhibitors of catalytically active memapsin 2 are expected to be particularly useful in the treatment and/or prevention of Alzheimer's disease. Thus, there is no evidence or data to show that a similar regimen can be used for treating a patient to decrease the likelihood of developing or the progression of Alzheimer's disease by administering to the individual an effective amount of a compound of claim 24 having an K_i of less than or equal to 10^{-7} M orally to block the cleavage of amyloid precursor protein in the manner claimed in claims 24-32.

Thus, in view of the above, and in view of the fact that there is no enablement in the instant specification for the method of treating and/or preventing of Alzheimer's disease by administering an effective amount of a compound of claim 24, and further in view of the complexity of Applicant's invention and the state of the art of treating and/or preventing of Alzheimer's disease; the Examiner is unable to determine the enablement of the invention as claimed without appropriate evidence or data. Such evidence in the art of treating cognitive dysfunctions details the state of the art in this area and establishes that even the disease is very hard to diagnose, let alone to treat and/or prevent. For example, Ezzell (Science News, pages 152-153, March 7, 1993) states on page 152, middle column, before last paragraph that doctors can only diagnose Alzheimer's through a process of elimination, ruling out other disorders such as a slight stroke, a brain tumor, or even an adverse drug reaction. A definitive diagnosis must await death and autopsy, when a pathologist can view the telltale "senile plaques" that pock the brains of Alzheimer's victim. Further, Varon et al. (Dev. Neurosci., Vol. 6, pp. 73-100, 1983/1984) discuss the implications of neurotrophic and neurite-promoting factor and their clinical potential in neuronal diseases such as Parkinson, ALS and Alzheimer in which the authors concluded by stating that further clinical progress requires a better understanding of neurobiological bases of nerve regeneration. Furthermore, Cordell et al. (U.S. Patent No. 5,221,607) discuss that the etiology of Alzheimer's disease is unknown and up to date, there are no means available to treat the pathogenesis of Alzheimer's disease and the paucity of understanding concerning the mechanism of amyloid formation in Alzheimer's disease is a major obstacle in the

development and design of therapeutic agents that can intervene in this process (See e.g., Col.1, lines 55-67). Similarly, Nelson et al. (U.S. Patent No. 5,252,463) discuss serious diseases affecting the central nervous system, which referred as neuropathologies such as Alzheimer's disease and Down's syndrome in which the etiology of Alzheimer's disease is unknown (See e.g., column 1).

Moreover, the current state of the art as discussed by WO 01/70672 (cited by Applicant on PTO-1449 under BA) which is published on 09/27/01 states on page 3, lines 8-11 that there is an urgent need for pharmaceutical agents capable of slowing the progression of Alzheimer's disease and/or preventing it in the first place; however, at present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. Furthermore, Hook (U.S. Patent No. 6,245,884) published on 06/12/01 states on col. 1, lines 49-55 that no methods of preventing Alzheimer's disease or Alzheimer's-type dementia (AD) is known and treatment is primarily is supportive, such as that provided by a family member in attendance. Simulated memory exercises on regular basis have been shown to slow, but not to stop, memory loss. A few drugs, such as tacrine, result in a modest temporary improvement of cognition but do not stop the progression of dementia. Therefore, the current state of the art clearly shows the unpredictable nature and the complexity of the art in regard to treatment of cognitive dysfunctions, which includes Alzheimer's disease. Thus, considering the nature of the treatment and/or prevention of Alzheimer's disease by administering an effective amount of inhibitor of memapsin 2 claimed and the limited success achieved; one skilled in the art would not accept the instantly claimed invention

as obviously valid and correct without demonstration of evidence or data for the following reasons:

In view of the fact that animals and humans are out bred, in view of the lack of disclosure of suitable animal models for a method of treating or preventing cell death in the central or peripheral nervous system, in view of the recognized problems in the art regarding effective treatment of diseases affecting the nervous systems (neuropathologies) and in view of the fact that it is difficult to regenerate the neurons in the living body; a reasonable doubt exists as to the enablement of the claimed method of treating and/or preventing Alzheimer's disease in a subject and particularly in a human by administering an effective amount of inhibitor of memapsin 2 claimed. Thus, the claims are based on pure speculation that the method would be effective since Applicant has not established any *nexus* between an effective amount of the claimed inhibitor of memapsin 2 and its use in the manner claimed.

Therefore, in view of the above and in view of the fact that there is no working example or data or evidence, which shows the claimed compounds, are useful as pharmaceutical formulations in the method of treatment as claimed in claims 24-32. Although, there is preparation Examples for pharmaceutical formulations as well as *in vitro* assays and certain mode of administration. Nevertheless there is no evidence in the instant specification to use or administer the pharmaceutical formulations in therapeutically effective amount as claimed, except for the mere recitation of protocols on pages 24-27 in the instant specification contemplating the suitable dosage of the compound to be administered generally in patients which includes human for the

intended treatment and/or prevention or slowing progression of Alzheimer's disease. Further, there are no sufficient data or evidence to substantiate such protocols of using pharmaceutical formulations of claim 24 I the manner claimed in claims 30-32. Hence, the only support for the claimed pharmaceutical formulation in the specification and method of treatment thereof is Applicant's supposition of the invention as recited in the protocols.

Thus, in view of the above, it would include those that have not been shown or taught to be useful or enabled by the disclosed method of making and using the invention. Further, undue experimentation is necessary to determine if and under what conditions, the claimed compound of claim 24 with the properties/characteristics recited in claims 25-29 in a method for treatment of a patient to decrease the likelihood of developing or the progression of Alzheimer's disease are contemplated and are encompassed as well various situations claimed. The results desired appear to be highly dependent on all variables, the relationship of which is not clearly disclosed. Hence, one of ordinary skill in the art would not be able to reproduce all the aspects of the claimed invention pharmaceutical formulations as well as methods for treatment and/or prevention of Alzheimer's disease as encompassed in the claims would be effective and under what conditions.

Therefore, in view of the above, the scope of the compound of claim 24is useful in a method for treating a patient to decrease the likelihood of developing or progression of Alzheimer's disease by administering to the individual an effective amount of memapsin 2 intended to be effective for the claimed purpose as encompassed in the

claims would be effective under what conditions. The Examiner is unable to determine the enablement of the invention as claimed without appropriate working examples. The only support for the claimed invention in the specification is Applicant's supposition of the invention and the protocols disclosed in the instant specification.

Further, the first paragraph of 35 U.S.C. 112 requires, *inter alia*, that a patent specification provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention without undue experimentation. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). While patent Applicants are not directed to disclose every species that falls within a generic claim, id. At 496, 20 USPQ2d at 1445, it is well settled that "the scope of the claims must bear a reasonable correlation to the scope of the enablement provided by the specification". *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Where practice of the full scope of the claims would require experimentation; factors to be considered in determining whether a disclosure would require undue experimentation ..... include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Therefore, in view of the above, and in view of the fact that there is no enablement in the instant specification for treating and/or preventing Alzheimer's disease by administering an effective amount of inhibitor of memapsin 2. Thus,

applying the *Wands* factors to the facts of this case, one of skill in the art would find that undue amount of experimentation would be required to practice the full scope of the extremely broad claims fro the reasons given above. Hence, in view of the quantity of experimentation necessary, the lack of adequate guidance or working examples or data, and the breadth of the claims, the claims are not commensurate in scope with the enabling disclosure. Accordingly, filing of evidence commensurate with the scope of the claims or amendment of the claims to what is supported by the enabling disclosure is suggested.

CITATION OF RELEVANT PRIOR ART

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Tang et al (U.S. Patent No. 6,545,127) disclose methods for the production of purified, catalytically active recombinant memapsin 2 including substrate analogues OMR99-1 and OMR99-2.

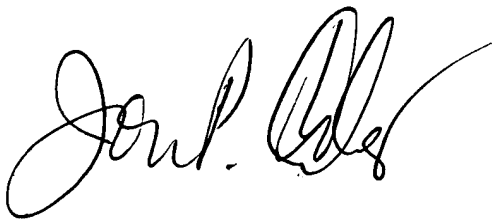
CONCLUSION AND FUTURE CORRESPONDENCE

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272 0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tsang Cecilia can be reached on (571) 272 0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Jon Weber
Supervisory Patent Examiner

/Mohamed/AAM
June 8, 2006